A new SPIN on horizontal transfer

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The regular and predictable inheritance of genetic material from parent to offspring is a cornerstone of the modern theory of evolutionary biology. However, most rules in biology are broken, at least sometimes. Horizontal gene transfer (HT) is the movement of genes between reproductively isolated species. It is common in prokaryotes, to the extent that some researchers refer to phylogenies of these species as a web, rather than a tree of life (1). In general, HT becomes progressively less frequent as organisms become more complex (2). However, there have been several well-documented examples of transfers involving both plants and animals (3). The vast majority of examples in complex animals have involved invertebrates (4). In this issue of PNAS, a new report (5) demonstrates the first evidence of recurrent HT among tetrapods, including several mammals.

As is so often the case when rules are broken, transposable elements, or transposons, are prime suspects. Many transposons have an extrachromosomal transposition intermediate and encode proteins that can permit integration into heterologous DNA. Further, after transfer, transposons can drive themselves into the recipient population even in the face of negative selective pressures (6, 7). HT of transposons has been well documented in invertebrates, where several classes of these mobile elements have been shown to have transferred between quite distantly related species (8). Indeed, based on these results it has been suggested that HT into naïve genomes is an essential feature of the transposon "life cycle," allowing them to enjoy brief periods of activity before becoming inactivated (9). Given the frequency of documented examples of HT of transposons between invertebrates, it is surprising that, until now, there have been no examples of transfer of these elements in mammals. However, the work by Feschotte and coworkers (5) clearly demonstrates HT of a DNA type transposon [SPACE INVADERS (SPIN) elements] into a variety of tetrapods, including tenrec, bushbaby, rat, mouse, bat, opossum, lizard, and frog, a diverse set of vertebrates that spans 360 million years of evolution.

HT has long been a contentious field. The sources of false identification of transferred genes can range from technical issues, such as the inadvertent placement of DNA sequence into the wrong database (more common than one might think), PCR mispriming or contamination, and incomplete sequence data, to methodological issues involving gene loss, incomplete species sampling, or poorly rooted phylogenies. Problems such as these have led to inflated claims for HT, most notoriously exemplified by an erroneous report of frequent HT from bacteria to humans (10). Thus, each claim for HT must be carefully scrutinized.

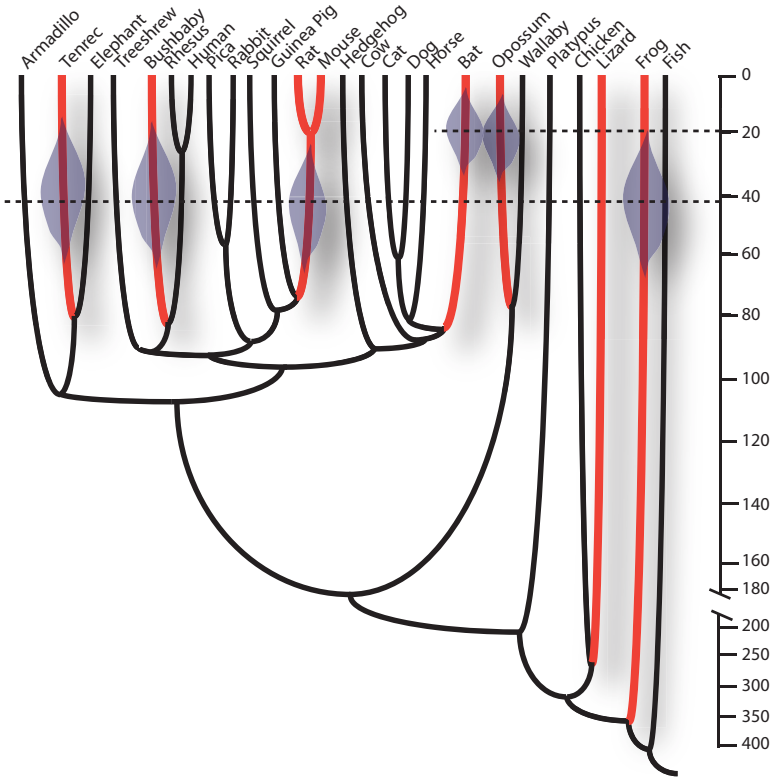

Fig. 1. A phylogeny of a variety of tetrapods illustrating incidences of HT. Lineages marked as red lines are those in which SPIN transposons were detected. The purple ovals represent the estimated time of HT as determined by the estimated age of the transposons in each species; estimates for lizard were not possible. Dashed lines represent estimated times of HTs. Time is expressed in millions of years.

One hallmark of HT is a patchy distribution. Among the tetrapods, Feschotte and coworkers (5) found such a pattern; the distribution of species that carry the SPIN transposons bears no resemblance to the phylogenic relationships of these species (Fig. 1). However, because transposons are generally selectively neutral or deleterious, the loss of an element from any given species is hardly unexpected, so patchiness by itself is only a clue that HT of a transposon has occurred. An unexpectedly high degree of sequence similarity can provide strong corroborating data. Feschotte and coworkers found that elements from species separated for hundreds of millions of years contained sequences that were more similar than some of the most conserved host genes. The similarity was in both coding and noncoding sites and cannot therefore be caused by selection on protein function. Further, with one notable exception, the elements were at different positions in each genome and were present in sometimes very large copy numbers. All copies, regardless of position, shared a high degree of sequence similarity with each other and with the elements in other species. Consensus sequences were derived for elements in each species by comparing

Author contributions: D.L. wrote the paper.
The author declares no conflict of interest.
See companion article on page 17023.
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multiple elements. These consensus sequences were nearly identical for all of the species examined, consistent with the transfer of the same or a highly similar transposon into a number of species. Collectively, these data strongly support the HT hypothesis; indeed they make the conclusion all but unavoidable.

Feschotte and coworkers (5) were able to date the insertion events by the clever use of older, vertically transmitted orthologous ancestral transposons present in humans and the other species at the same chromosomal locations. These are transposons that are no longer functional but that remain as "molecular fossils," whose sequences degrade over time as a function of the neutral mutation rate. By comparing the degree of divergence of these fossils with the known divergence time of pairs of species, it was possible to calibrate the molecular clocks. Using this calibration, the average time required to result in the observed divergence between elements in a given species could be determined, resulting in a rough estimate of the time of horizontal transfer. Five species (tenrec, bushbaby, rat, mouse, and frog) showed evidence of a HT at roughly the same time, ≈40 million years ago, nearly an order of magnitude more recent that the last common ancestor of these species. This is a remarkable and unexpected finding, because it suggests that the ancestors of these species, some of which occupied different continents, were infiltrated by the same transposon at roughly the same time.

As is often the case with HT, these results raise far more questions than they answer. Most notably, why those species, why then, and how did the transposon get into their germ lines? No one knows the answer to these questions for these or any other HTs among eukaryotes. Certainly there are many potential vectors (viruses, for instance), and ecological factors are likely to have been important. This was true of HT into *Drosophila melanogaster*, which experienced at least 3 transposon invasions in the 200 years after the introduction of this species from the Old World to the New World (11). The problem is a difficult one, because the conditions making HT possible in any given situation may be the result of extremely rare and fortuitous combinations of factors that are no longer detectable. If, for instance, a particular vector was important, that vector may now be extinct. It is likely that we will never know how the transfer of SPIN elements occurred 40 million years ago. To determine the mechanism of HT, the best strategy would be to find one that occurred very recently, because the variables necessary for that transfer are still accessible to examination. Given the rate at which human activity has brought together previously isolated species together over the past few hundred years (12), there may be an unprecedented number of HTs waiting to be detected in extant populations.

When active, transposons can be extraordinarily effective mutagens.

It is clear that transposons are particularly prone to HT. Why should we care? Because transposons spread within population largely because of their replication advantage over other genes, they are generally selectively neutral or slightly deleterious (13). Thus, HT of transposons may represent a relatively unimportant phenomenon, at least from the point of view of the host. However, it should be noted that HT of transposons is often associated with dramatic increases in transposon activity. The star phylogeny apparent in the tetrapod SPIN elements is consistent with a relatively brief period of intense activity, and the same is true of well-documented examples of HT among invertebrates (14). When active, transposons can be extraordinarily effective mutagens (15). Their effects range from small deletions and subtle changes of gene expression to massive chromosomal rearrangements (16). Thus, HT of transposons can result in the activation of a potent mutagen that can promote rapid changes in genome structure and gene function. Regular invasions by transposons would be expected to be associated with regular spikes in mutation rates, which could in turn lead to reproductive isolation of subpopulations (because of chromosomal inversions for instance), or the appearance of advantageous new mutations. If we accept the proposition that transposon activity is a potent source of potentially useful variation, then HT of these selfish genetic elements may have had profound impact on the evolution of their hosts.

ACKNOWLEDGMENTS. In D.L.'s laboratory, work on transposable elements is supported by National Science Foundation Grant DBI 0820828.

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